Long-term data from the Swiss pulmonary hypertension registry

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Abstract: Background: Registries are important for real-life epidemiology on different pulmonary hypertension (PH) groups. Objective: To provide long-term data of the Swiss PH-registry 1998-2012. Methods: PH-patients were classified in 5 groups and registered upon written informed consent at 5 University- and 8 associated hospitals since 1998. NYHA, 6 minute walk distance, hemodynamics and therapy were registered at baseline. Patients were regularly followed and therapy and events (death, transplantation, endarterectomy or lost to follow-up) registered. The data was stratified according to the time of diagnosis into prevalent before 2000 and incident during 2000-04, 2005-08 and 2009-12. Results: From 996 (53% female) PH-patients, 549 had pulmonary arterial hypertension (PAH), 36 PH due to left heart -, 127 due to lung disease, 249 chronic thromboembolic PH (CTEPH) and 35 miscellaneous PH. Age and BMI significantly increased over time whereas hemodynamic severity decreased. Overall, event-free survival was 84, 72, 64, 58% for the years 1-4 and similar for time periods since 2000, but better during the more recent periods for PAH and CTEPH. 89% of all PAH had target medical therapy, 43% combination-therapy. 14 resp. 2% of CTEPH underwent pulmonary endarterectomy or transplantation, 87 % were treated with PAH-target therapy. Conclusion: Since 2000, incident Swiss PH-patients registered were older, hemodynamically better and mostly treated with PAH-target therapies. Survival was better for PAH and CTEPH diagnosed since 2008 compared with earlier diagnosis or other classifications.

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Long-Term Data from the Swiss Pulmonary Hypertension Registry

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Key Words

Registry · Pulmonary hypertension · Pulmonary arterial hypertension · Chronic thromboembolic pulmonary hypertension

Abstract

Background: Registries are important for real-life epidemiology on different pulmonary hypertension (PH) groups. ***Objective:*** To provide long-term data of the Swiss PH registry of 1998–2012. ***Methods:*** PH patients have been classified into 5 groups and registered upon written informed consent at 5 university and 8 associated hospitals since 1998. New York Heart Association (NYHA) class, 6-min walk distance, hemodynamics and therapy were registered at baseline. Patients were regularly followed, and therapy and events (death, transplantation, endarterectomy or loss to follow-up) registered. The data were stratified according to the time of diagnosis into prevalent before 2000 and incident during 2000–2004, 2005–2008 and 2009–2012. ***Results:*** From 996 (53% female) PH patients, 549 had pulmonary arterial hypertension (PAH), 36 PH due to left heart disease, 127 due to lung disease, 249 to chronic thromboembolic PH (CTEPH) and 35 to miscellaneous PH. Age and BMI significantly increased over time, whereas hemodynamic severity decreased. Overall, event-free survival was 84, 72, 64 and 58% for the years 1–4 and similar for time periods since 2000, but better during the more recent periods for PAH and CTEPH. Of all PAH cases, 89% had target medical therapy and 43% combination therapy. Of CTEPH patients, 14 and 2% underwent pulmonary endarterectomy or transplantation, respectively; 87% were treated with PAH target therapy. ***Conclusion:*** Since 2000, the incident Swiss PH patients registered were older, hemodynamically better and mostly treated with PAH target therapies. Survival has been better for PAH and CTEPH diagnosed since 2008 compared with earlier diagnosis or other classifications.

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Introduction

Pulmonary hypertension (PH) is classified into 5 major groups [1, 2]. Group I or pulmonary arterial hypertension (PAH) might be idiopathic, hereditary or associated with different disorders. Group II involves the postcapillary PH forms due to left heart diseases. Group III encompasses PH due to chronic hypoxemic lung diseases, group IV chronic thromboembolic PH (CTEPH) and group V PH due to unclear/multifactorial mechanisms. Many forms of PH share a final common pathway and response to treatment [3, 4]. CTEPH is mostly preceded by venous thromboembolism and might be cured by surgical endarterectomy in selected patients [5]. Distal CTEPH shares pathogenetic and clinical features with PAH [4, 5].

The epidemiology of PH is still incompletely known [6]. Registries have given information on some aspects of the disease in different parts of the world, but only few registries included patients with different PH classifications [7–14]. The first registry providing data on primary PH, today named idiopathic PAH, was the NIH registry including 194 patients from 1981 to 1988 in 32 US centers [15]. Other nationwide registries followed, mainly including patients with PAH or CTEPH, with follow-up periods up to 8 years [8, 10, 16, 17]. The first long-term registry on different PH groups was the ASPIRE registry, a single-center registry from Sheffield with a follow-up of up to 10 years [7]. Switzerland was one of the first countries to set up a nationwide registry in 1998, when the first prevalent cases were included followed by incident cases from 2000. The Swiss registry focused on PAH and CTEPH; however, the inclusion of patients with other PH classifications was allowed [12, 18]. The Swiss registry has been run for ≥15 years and provides an opportunity to compare the course of incident patients over different time periods and to investigate the changing epidemiology of PH.

Methods

The Swiss registry was opened in 1998, and data were prospectively collected in 5 university and in 8 associated hospitals. The registry focuses on PAH and CTEPH but allows entering data from all PH types confirmed by right heart catheterization. All patients gave their written informed consent, and the registry was approved by the Swiss Agency on Registries.

Patients included in the registry were classified into 5 major groups. Despite changes in classification over the years, these groups still mainly correspond to the current classification [1, 2, 19]: group I = PAH including idiopathic/hereditary PAH (the two were not distinguished), induced by drugs and toxins, associated with connective tissue disease, HIV infection, portal hypertension, congenital heart diseases and others; group II = PH due to left heart disease; group III = PH due to lung diseases/hypoxia; group IV = CTEPH, and group V = miscellaneous [1]. The classification was done according to guidelines [20]; all patients had diagnostic right heart catheterization including measurement of pulmonary artery wedge pressure to confirm and classify PH into pre- and postcapillary groups [20]. All patients had a thorough clinical investigation including ventilation-perfusion scan, echocardiography, pulmonary function test, thoracic computed tomography and/or pulmonary angiography, blood analysis and more according to the clinical picture to correctly classify patients [19]. Each center was responsible for allocating their patients to one of the respective PH classifications.

Mandatory data at baseline were: classification, demographics, vital functions, functional parameters (New York Heart Association, NYHA class; 6-min walk distance, 6MWD; Borg scale), the tricuspid gradient and the following hemodynamics by heart catheterization: mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure, right atrial pressure, cardiac output, mixed venous oxygen saturation and vasoreactivity defined as a decrease in pulmonary vascular resistance (PVR) ≥20% (until 2005) or mPAP ≥10 to ≤40 mm Hg. After baseline diagnosis, patients were regularly followed, and the following information was registered: PAH target therapy defined as endothelin receptor antagonists (ERA), phosphodiesterase inhibitors (PDE5-I) or prostanoids; therapy with calcium channel blockers (CCB) given for PAH was noted separately, and the times of events defined as death, lung transplantation or loss to follow-up (date last alive) such as pulmonary endarterectomy were entered.

In 2012 the event status of every registered patient was checked, and data were extracted for analysis by December. Analysis was performed overall and separately for PAH, CTEPH and other groups with >100 data sets. The following time periods for analysis were defined: up to end of 1999 (including incident and prevalent cases), incident cases diagnosed in 2000–2004, 2005–2008 and 2009–2012. Death, lung transplantation, pulmonary endarterectomy and the date when the patient was last observed alive in case of loss to follow-up were considered as events for survival analysis.

Analyses were performed using SPSS Statistics version 21. Data are presented as means (with standard deviations) or numbers (with percentages). ANOVA, the t test or Mann-Whitney U test was used. Lifetable, Kaplan-Meier analysis and Cox regression were performed to compare event-free survival and impact of covariates overall and according to period of diagnosis. A $p < 0.05$ was considered significant.

Results

Overall PH Patients

The patients' flowchart is shown in figure 1. From 1,119 data sets retrieved from the registry, 68 had to be excluded as main parameters (classification or mPAP) were missing. Fifty-five patients did not fulfil diagnostic criteria. Baseline characteristics of the final 996 patients overall or stratified by the predefined diagnostic time periods are shown in table 1.

Table 1. Overall PH classifications

	Overall	Before 2000	2000–2004	2005–2008	2009–2012	p
Demographics						
Number of patients	996	39	227	365	365	
Females	533 (54)	20 (51)	128 (56)	198 (54)	187 (51)	
Children and adolescents (<18 years)	36 (3.6)	6 (15.4)	16 (7)	11 (3)	3 (0.8)	
Age, years	58.4±17.8	38.5±20.1	53.0±19.4	59.8±16.8	62.5±15.0	0.000
BMI	26.3±6.4	23.9±6.5	26.0±8.0	26.2±5.8	26.9±5.9	0.045
Classification						
PAH	549 (55.1)	30 (76.9)	147 (64.8)	201 (55.1)	171 (46.8)	
PH due to left heart disease	36 (3.6)	1 (2.6)	2 (0.9)	12 (3.3)	21 (5.8)	
PH due to lung disease	127 (12.8)	0	19 (8.4)	52 (14.2)	56 (15.3)	
CTEPH	249 (25)	8 (20.5)	52 (22.9)	89 (24.4)	100 (27.4)	
Miscellaneous	35 (3.5)	0	7 (3.1)	11 (3)	17 (4.7)	
Characteristics						
mPAP, mm Hg	46±14	55±16	50±16	45±12	44±12	0.000
Cardiac index (n = 883), l/min/m^2	2.5±0.9	3.0±1.7	2.5±0.8	2.5±0.8	2.6±0.8	0.000
NYHA class mean (n = 864)	2.9±0.7	2.8±0.7	3.1±0.7	2.9±0.7	2.9±0.7	0.01
6MWD (n = 799), m	357±137	323±125	362±136	365±133	350±143	0.392
Outcome by December 31, 2012						
Follow-up days	1,346±1,286	4,104±2,867	1,889±1,402	1,464±833	595±416	
Alive	528 (53)	19 (45)	64 (28)	176 (48)	269 (74)	
Dead	329 (33)	12 (31)	124 (55)	137 (38)	56 (15)	
Lung transplantation	38 (4)	5 (13)	17 (8)	12 (3)	4 (1)	
Pulmonary endarterectomy	36 (4)	0	7 (3)	12 (3)	17 (5)	
Lost to follow-up	65 (7)	3 (8)	15 (7)	28 (8)	19 (5)	

Data are given as means ± SD or numbers with percentages in parentheses.

Over consecutive periods, fewer patients with PAH but more patients with other classifications were included (fig. 2). Age at diagnosis, BMI and blood pressure significantly increased over time, and mPAP and PVR decreased. The cardiac index remained stable over the last 3 incident periods, whereas it was higher during the first period which included younger and mostly prevalent patients. In the period from 2000 to 2004, newly diagnosed incident cases had the worst WHO functional class (table 1).

The absolute follow-up time from diagnosis to the end of 2012 or an event ranged from 1 to 10,378 days (>28 years). The longest follow-up was observed in a patient diagnosed in 1984 at the age of 37 years with idiopathic vasoreactive PAH, who was successfully treated with CCB. The percentage of lung transplantation decreased over time. Endarterectomy in CTEPH was rare but slightly increased over time.

The 1- to 4-year event-free-survival over all PH groups was similar during the 3 incident periods, and best for the

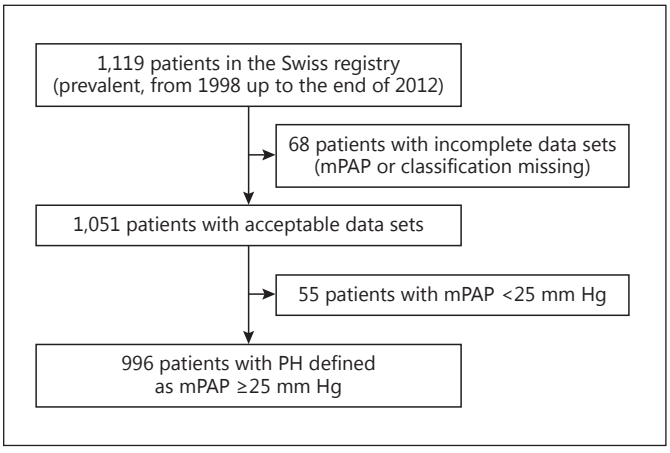

Fig. 1. Flowchart of patient data set selection.

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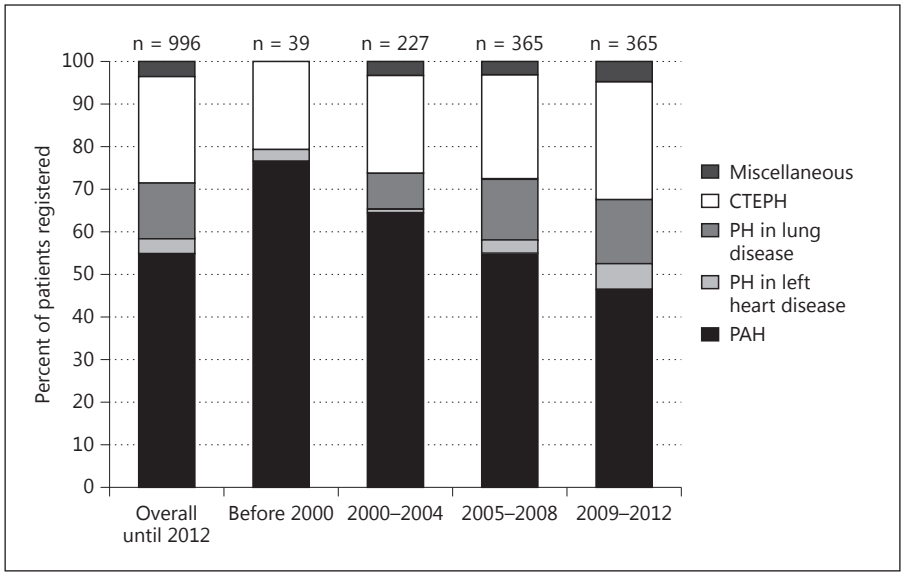

Fig. 2. Distributions of PH diagnostic groups by time of diagnosis.

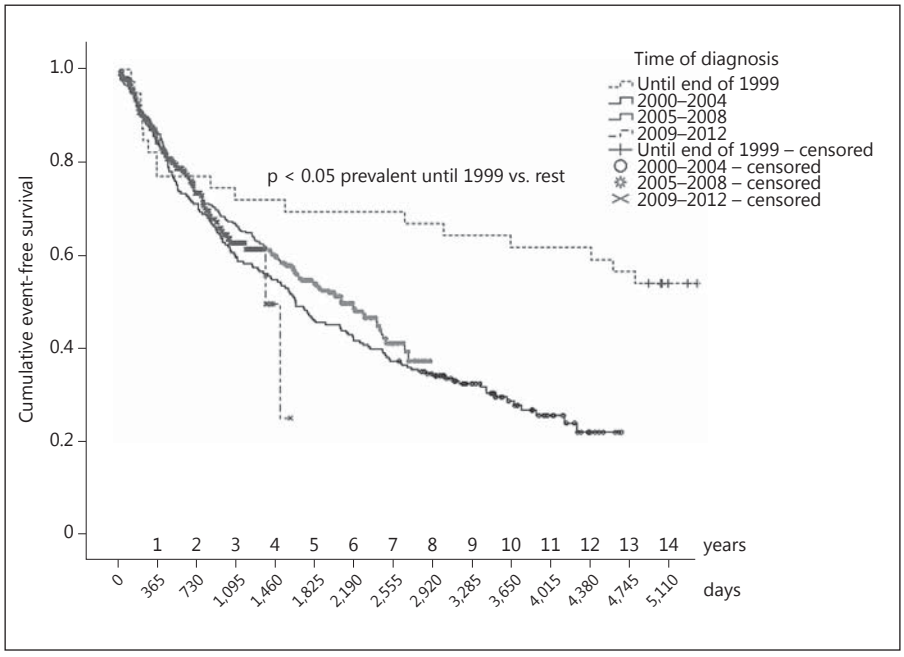

Fig. 3. Kaplan-Meier survival curves according to the time of diagnosis.

first period, where prevalent cases were registered. Cumulative survival up to 12 years shows an equal survival for incident cases diagnosed in 2000–2012, but better survival for prevalent cases diagnosed before 2000 (fig. 3).

Overall, 68% of all patients were treated with PAH target therapy during the first 3 months after diagnosis; hereof 9% received combination therapy (table 1). A total of 85% received PAH target therapy for >3 months of the entire observation period; hereof 41% received combination therapy.

Adult Patients with PAH

Among the 549 patients with PAH (group I), 517 were ≥18 years (60% women; table 2). Patients diagnosed more recently were significantly older than those diagnosed earlier. Overall, 60% suffered from idiopathic PAH, with an increasing percentage over time. The overall mPAP was 48 ± 15 mm Hg and was significantly lower during the last periods. Other hemodynamic and blood oxygenation parameters were comparable over time. Vasoreactivity testing was performed in 274/517 (53%) PAH pa-

Table 2. Patients with PAH

	Overall	Before 2000	2000–2004	2005–2008	2009–2012	p
Demographics						
Number of patients	517	24	131	191	171	
Females	309 (60)	16 (63)	83 (63)	116 (61)	95 (56)	
Age, years	57±16	42±16	53±16	59±16	60±15	0.000
BMI	26±7	25±6	27±9	27±6	26±6	0.575
Classification						
Idiopathic	308 (60)	12 (50)	65 (50)	113 (59)	102 (60)	
Drug- and toxin-induced	10 (2)	2 (8)	2 (2)	4 (2)	2 (1)	
Connective tissue diseases	94 (18)	5 (21)	31 (24)	30 (16)	28 (16)	
HIV-associated	34 (7)	2 (8)	2 (2)	8 (4)	13 (8)	
Portopulmonary	26 (5)	1 (4)	4 (3)	10 (5)	11 (6)	
Congenital heart disease	41 (8)	2 (8)	13 (10)	16 (8)	10 (6)	
Other (telangiectasia, storage)	7 (1)	0	4 (3)	3 (2)	0	
Pulmonary veno-occlusive disease	12 (2)	0	1 (1)	7 (4)	4 (2)	
Pulmonary capillary hemangiomatosis	1 (0)	0	0	0	1 (1)	
Vital signs and hemodynamics						
Heart rate (n = 469), bpm	82±15	83±14	82±13	83±15	81±16	0.793
Tricuspid gradient (n = 331), mm Hg	67±20	79±23	69±19	64±18	68±22	0.34
mPAP (n = 517), mm Hg	48±15	55±18	51±17	46±14	46±12	0.000
Pulmonary artery wedge pressure (n = 466), mm Hg	12±7	12±8	12±7	12±7	12±7	0.963
Right atrial pressure (n = 425), mm Hg	9±4	9±4	10±8	9±6	9±8	0.511
PVR (n = 440), dyn/s/m^5	753±445	811±431	833±417	756±502	680±418	0.057
Cardiac index (n = 439), l/min/m^2	2.5±0.8	2.6±0.9	2.5±0.9	2.4±0.8	2.6±0.8	0.345
Arterial oxygen saturation (n = 445), %	93±5	94±4	92±5	92±5	93±5	0.161
Mixed venous oxygen saturation (n = 399), %	63±10	66±12	62±11	62±10	64±10	0.213
Vasoreactivity positive (n = 274)	88±32	6±40	32±43	38±36	12±15	
Functional capacity						
NYHA class (n = 450)						
I	5 (1)	1 (4)	1 (1)	3 (2)	0	
II	109 (24)	6 (25)	23 (19)	32 (21)	48 (32)	
III	259 (57)	15 (63)	73 (59)	94 (61)	77 (52)	
IV	77 (17)	2 (8)	26 (21)	25 (16)	24 (16)	
NYHA mean (n = 450)	2.9±0.6	2.8±0.7	3.0±0.7	2.9±0.7	2.8±0.7	0.129
6MWD (n = 423), m	362±137	341±120	364±144	360±133	366±139	0.916
Outcome by December 31, 2012						
Follow-up days	1,393±1,337	4,021±3,035	1,832±1,379	1,483±826	588±420	
Alive	271 (52)	12 (50)	35 (27)	94 (49)	130 (76)	
Dead	191 (37)	7 (29)	79 (60)	79 (41)	26 (15)	
Lung transplantation	20 (4)	4 (17)	10 (8)	4 (2)	2 (1)	
Lost to follow-up	34 (7)	1 (4)	6 (5)	14 (7)	13 (8)	

Data are given as means ± SD or numbers with percentages in parentheses.

tients. 32% of tested patients fulfilled criteria of acute vasoreactivity, with patients diagnosed within the last 4 years showing lower vasoreactivity (15%).

After an overall mean follow-up time of 1,393 ± 1,337 days (3.8 years; table 2), 191/517 patients died, 20 had lung transplantation and 34 were lost to follow-up. The overall survival at 1, 2, 3 and 4 years was 87, 77, 69 and 64%, respectively, with a better 4-year survival for patients diagnosed in 2009–2012 compared with 2005–2008 and 2000–2004 (73 vs. 66 and 54%, p = 0.02, 0.824 and 0.03, respectively). The cumulative transplant-free survival for incident PAH patients diagnosed from 2000 is higher for more recent time periods (fig. 4).

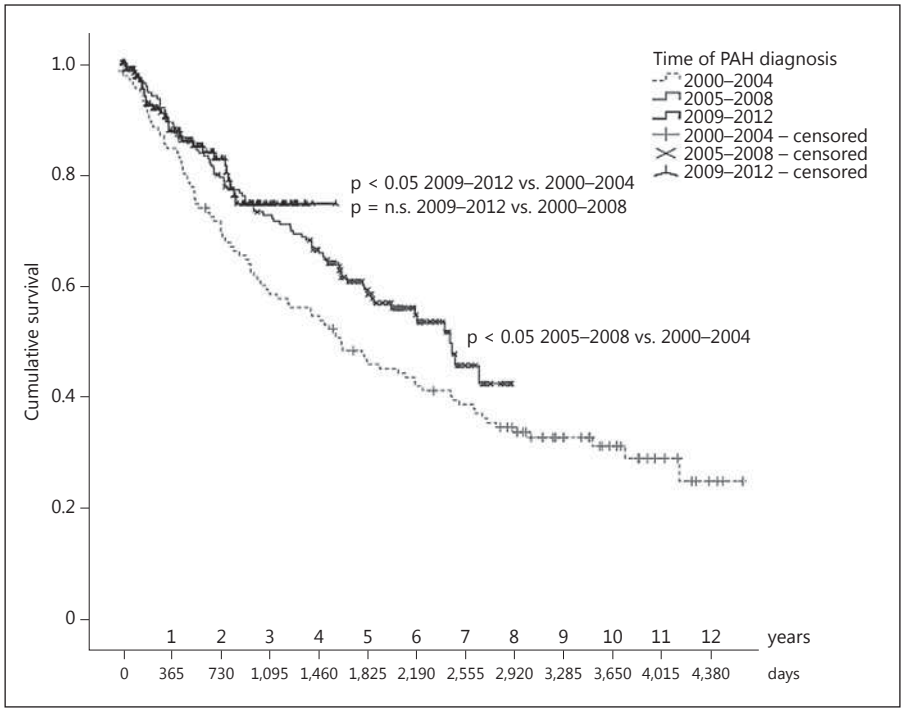

Fig. 4. Kaplan-Meier survival curves for incident PAH during different time periods.

Table 3. Target therapy in patients with PAH

	Overall	Before 2000	2000–2004	2005–2008	2009–2012
Patients	517	24	131	191	171
Therapy started within 3 months					
No target therapy	146 (28)	16 (63)	47 (40)	53 (28)	31 (18)
High-dose CCB	36 (7)	6 (25)	8 (6)	15 (8)	7 (4)
Single drug	303 (59)	9 (38)	72 (55)	115 (60)	107 (63)
Double combination	51 (10)	0	10 (8)	17 (9)	24 (14)
Triple combination	17 (3)	0	2 (2)	6 (3)	9 (5)
ERA	269 (52)	0	52 (40)	112 (59)	105 (61)
Prostanoids	73 (14)	9 (8)	40 (31)	12 (6)	12 (7)
PDE5-I	113 (22)	0	6 (5)	42 (22)	65 (38)
Maximal therapy					
No PAH target therapy	55 (11)	4 (17)	18 (14)	21 (11)	12 (7)
High-dose CCB	25 (5)	3 (12)	9 (7)	10 (5)	3 (2)
Single drug	236 (46)	9 (38)	55 (42)	85 (45)	87 (51)
Double combination	152 (29)	10 (42)	36 (28)	53 (28)	53 (31)
Triple combination	74 (14)	1 (4)	22 (17)	32 (17)	19 (11)

Data are numbers with percent of total in parentheses.

72% of PAH patients received first-line PAH target therapy within 3 months of diagnosis with increasing percentages over time (table 3). The majority was started on a single drug, 10% received double and 3% triple combination therapy with an increasing percentage over time. 1/4 of the 28% of patients who did not receive PAH target therapy received a high-dose CCB (overall 7%), with a decreasing percentage over time (table 3). From patients diagnosed with positive vasoreactivity testing in 2000–2004, 2005–2008 and 2009–2012, 25, 39 and 58% received

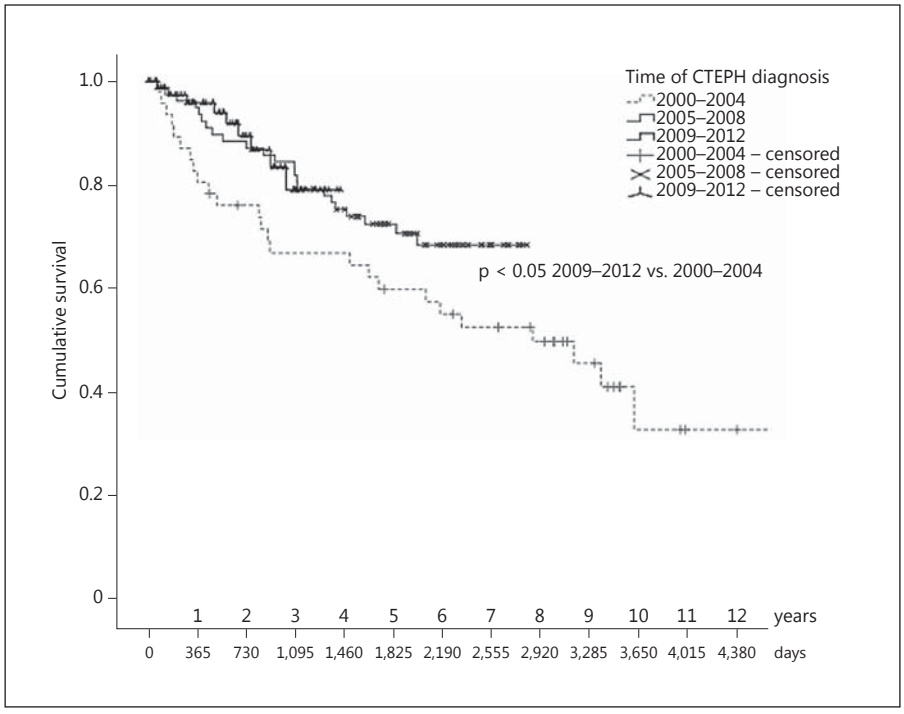

Fig. 5. Kaplan-Meier survival curves of 215 nonoperated CTEPH patients according to their time of diagnosis.

first-line CCB, respectively. During follow-up, 89% of all patients received PAH target therapy, 29 and 14% received double or triple combination therapy, respectively.

Patients with CTEPH

All 249 patients with CTEPH were >18 years old with equal sex distribution (table 4). Mostly, proximal/surgically accessible or distal/surgically inaccessible disease was not distinguished. Patients were severely compromised with a mean mPAP of 45 ± 12 mm Hg, PVR of 767 ± 463 dyn/s/m^5, NYHA/WHO class 3 ± 0.7 and 6MWD of 365 ± 138 m with equal limitation since 2000. The overall mean follow-up time of CTEPH was 1,313 days (range 1–7,618). 14 and 2% of patients had pulmonary endarterectomy or lung transplantation, respectively, 23% died and 6% were lost to follow-up. The overall 1-, 2-, 3- and 4-year transplant-free survival in nonoperated CTEPH was 91, 84, 77 and 73%, respectively and better recently (fig. 5).

Adult Patients with PH in Chronic Lung Disease

127 subjects had PH due to lung diseases, with a mean age of 66 ± 12 years, 31% females, all incident in 2000–2012 (table 5). 29% had obstructive and 28% interstitial lung diseases, a minority sleep-disordered breathing, hypoventilation or developmental disease. 31% were not further classified. Overall, mPAP was 41 ± 11 mm Hg, PVR 515 ± 346 dyn/s/m^5, NYHA class 3 ± 0.7 and 6MWD 305 ± 126 m. The transplant-free 1- to 4-year survival was 79, 62, 52 and 45%, respectively. Overall, 71% were treated with PAH target therapy (50% single, 23% combination therapy). Kaplan-Meier analysis revealed equal survival for patients with and without PAH target therapy.

Differential Aspects between Different PH Groups

Characteristics of PH patients by diagnostic groups are shown in table 5. Patients with CTEPH were significantly older and more obese compared with PAH cases and had lower mPAP, cardiac index and arterial oxygen saturation. Functional class and the 6MWD were equal in PAH and CTEPH. Event-free survival by Kaplan-Meier analysis and lifetable was similar in PAH and CTEPH, but worse in PH due to lung disease and miscellaneous forms (table 6; fig. 6).

Discussion

The Swiss PH registry was opened in 1998 and provides long-term data of patients seen at PH referral centers throughout Switzerland. During the first 2 years, prevalent and incident PH cases and from 2000 only in-

Table 4. Patients with CTEPH

	Overall	Before 2000	2000–2004	2005–2008	2009–2012	p
Demographics						
CTEPH	249	8	52	89	100	
Females	129 (52)	2 (33)	27 (50)	50 (56)	50 (50)	
Age, years	63±14	49±16	62±13	63±13	64±15	0.02
BMI	27.0±5.1	25.8±4.1	26.9±5.5	26.4±4.5	27.7±5.3	0.31
CTEPH classification						
Proximal disease	22 (9)	1 (13)	10 (19)	3 (3)	8 (8)	
Distal disease	29 (12)	3 (38)	11 (21)	4 (5)	11 (11)	
Not classified	198 (80)	4 (50)	31 (60)	82 (92)	81 (81)	
Vital signs and hemodynamics						
Heart rate (n = 235), bpm	81±14	79±12	18±16	78±13	83±14	0.132
Tricuspid gradient (n = 146), mm Hg	66±18	71±9	67±18	64±20	67±16	0.728
mPAP (n = 249), mm Hg	45±12	52±12	47±15	44±10	45±12	0.305
Pulmonary artery wedge pressure (n = 233), mm Hg	12±6	17±13	12±7	11±6	12±4	0.06
Right atrial pressure (n = 223), mm Hg	9±6	11±6	9±6	9±5	9±7	0.784
PVR (n = 218), dyn/s/m^5	767±463	902±620	805±442	765±476	740±457	0.798
Cardiac index (n = 227), l/min/m^2	2.3±0.6	2.2±0.7	2.1±0.4	2.4±0.6	2.3±0.7	0.086
Arterial oxygen saturation (n = 229), %	92±4	87±9	91±4	93±3	93±4	0.0
Mixed venous oxygen saturation (n = 203), %	60±10	57±15	58±8	59±10	62±11	0.149
Functional capacity						
NYHA class mean (n = 228)	3.0±0.7	3.4±0.5	3.1±0.7	2.9±0.6	2.9±0.7	0.109
6MWD (n = 214), m	365±138	279±140	356±117	394±133	348±148	0.74
Outcome by December 31, 2012						
Follow-up days until event or December 2012	1,313±1,158	2,905±3,046	1,911±1,372	1,626±797	596±411	
Alive (without operation)	138 (55)	1 (13)	16 (31)	50 (56)	71 (71)	
Dead	58 (23)	4 (50)	23 (44)	22 (25)	9 (9)	
Lung transplantation	4 (2)	1 (13)	2 (4)	1 (1)	0	
PEA	34 (14)	0	6 (12)	12 (14)	16 (16)	
Days until PEA	644±582	–	978±622	774±720	421±352	
Lost to follow-up	15 (6)	2 (25)	5 (10)	4 (5)	4 (4)	
Target therapy						
Therapy started within 3 months						
No drug	68 (27)	38 (3)	14 (27)	25 (28)	26 (26)	
Single drug	160 (65)	5 (63)	37 (71)	54 (61)	64 (64)	
Double combination	19 (8)	0	1 (2)	9 (10)	9 (9)	
Triple combination	1 (0.4)	0	0	1 (1)	0	
ERA	123 (49)	0	11 (4)	49 (20)	63 (63)	
Prostanoid	33 (13)	5 (2)	27 (11)	1 (0.4)	0	
PDE5-I	47 (19)	0	2 (1)	25 (10)	20 (20)	
Maximal therapy						
No drug	30 (12)	2 (25)	6 (12)	4 (5)	18 (18)	
Single drug	110 (44)	4 (50)	19 (37)	38 (43)	49 (49)	
Double combination	85 (34)	1 (13)	16 (31)	38 (43)	30 (30)	
Triple combination	23 (9)	1 (13)	11 (21)	9 (10)	2 (2)	

PEA = Pulmonary endarterectomy. Data are given as means ± SD or numbers with percentages in parentheses.

Table 5. PH due to chronic lung diseases

	Overall	2000–2004	2005–2008	2009–2012	p
Demographics					
PH in lung disease	127	19	52	56	
Females	39 (31)	6 (32)	13 (25)	20 (36)	
Age, years	66±12	63±11	66±13	67±12	0.488
BMI (n = 120)	276	28±5	27±6	28±6	0.672
Lung disease classification					
Not further classified	39 (31)	4 (21)	15 (29)	20 (36)	
Obstructive	37 (29)	6 (32)	15 (29)	16 (29)	
Interstitial	35 (28)	7 (37)	16 (31)	12 (21)	
Sleep disorders	6 (5)	1 (5)	2 (4)	3 (5)	
Hypoventilation	7 (6)	1 (5)	3 (6)	3 (5)	
Developmental	3 (2)	0	1 (2)	2 (4)	
Vital signs and hemodynamics					
Heart rate (n = 116), bpm	87±20	93±21	85±16	86±22	0.379
Tricuspid gradient (n = 76), mm Hg	61±20	73±27	56±15	60±19	0.020
mPAP (n = 127), mm Hg	41±11	45±12	39±9	41±12	0.142
Pulmonary artery wedge pressure (n = 121), mm Hg	13±7	12±8	14±8	12±5	0.202
Right atrial pressure (n = 115), mm Hg	9±9	9±7	8±5	11±12	0.167
PVR (n = 109), dyn/s/m^5	515±346	706±388	424±320	605±402	0.010
Cardiac index (n = 119), l/min/m^2	2.6±0.6	2.6±0.6	2.6±0.7	2.6±0.6	0.848
Arterial oxygen saturation (n = 112), %	89±8	85±13	90±8	89±5	0.052
Mixed venous oxygen saturation (n = 102), %	62±11	59±16	62±10	62±9	0.46
Functional capacity					
NYHA class mean (n = 101)	3.0±0.7	3.3±0.7	3.1±0.7	2.8±0.7	0.035
6MWD (n = 100), m	305±126	306±138	332±115	279±129	0.145
Outcome by December 31, 2012					
Follow-up days	979±870	1,425±1,410	1,236±831	589±395	
Alive	59 (47)	1 (5)	21 (40)	37 (66)	
Dead	52 (41)	13 (68)	24 (46)	15 (27)	
Lung transplantation	8 (6)	3 (16)	3 (6)	2 (4)	
Lost to follow-up	8 (6)	2 (11)	4 (8)	2 (4)	
Target therapy					
Therapy started within 3 months					
No drug	55 (43)	6 (32)	27 (52)	22 (39)	
Single drug	65 (51)	12 (63)	24 (46)	29 (52)	
Double combination	7 (6)	1 (5)	1 (2)	5 (9)	
Triple combination	0	0	0	0	
ERA	44 (35)	8 (42)	17 (33)	19 (34)	
Prostanoid	8 (6)	4 (21)	3 (6)	1 (2)	
PDE5-I	27 (21)	2 (11)	6 (12)	19 (34)	
Maximal therapy					
No drug	36 (28)	3 (16)	8 (35)	15 (27)	
Single drug	62 (50)	8 (42)	25 (48)	29 (52)	
Double combination	24 (19)	7 (37)	8 (15)	9 (16)	
Triple combination	5 (4)	1 (5)	1 (2)	3 (5)	

Data are given as means ± SD or numbers with percentages in parentheses.

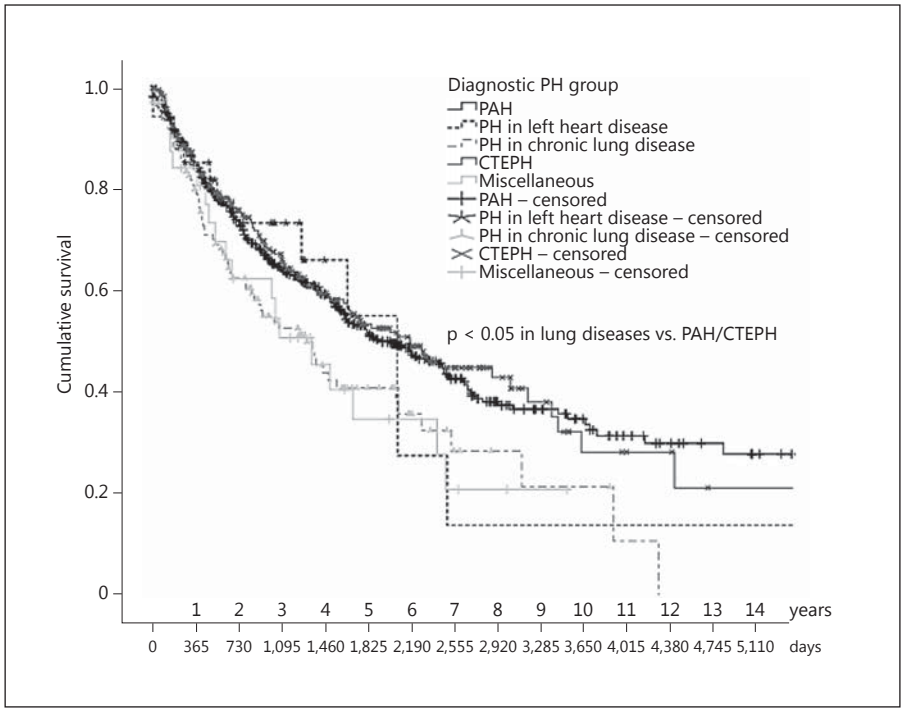

Fig. 6. Kaplan-Meier survival curves by diagnosis for adult patients with PH by their diagnostic group.

Table 6. Adult patients by diagnostic group

	PAH (group I)	Left heart disease (group II)	Lung disease (group III)	CTEPH (group IV)	Miscellaneous (group V)	p value	
						overall	PAH vs. CTEPH
Demographics							
Number	517	35	125	249	35		
Females	309 (60)	23 (66)	37 (30)	120 (48)	12 (34)		
Age, years	57±16	62±15	67±10	63±13	59±15	0.000	0.000
BMI (n = 120)	26±7	29±7	27±6	27±5	24±5	0.026	0.009
Vital signs and hemodynamics							
Heart rate (n = 873), bpm	82±15	77±35	87±20	81±14	83±16	0.005	0.723
Tricuspid gradient (n = 593), mm Hg	67±20	61±15	61±20	66±18	60±13	0.036	0.371
mPAP (n = 960), mm Hg	48±16	42±12	40±10	45±12	42±11	0.000	0.022
Pulmonary artery wedge pressure (n = 883), mm Hg	12±7	20±7	13±7	12±6	13±6	0.000	0.04
Right atrial pressure (n = 820), mm Hg	9±8	10±5	9±9	9±6	8±5	0.937	0.949
PVR (n = 821), dyn/s/m^5	753±454	413±238	545±345	767±463	604±446	0.000	0.742
Cardiac index (n = 847), l/min/m^2	2.5±0.8	2.7±0.8	2.6±0.6	2.3±0.6	3.0±1	0.000	0.000
Arterial oxygen saturation (n = 837), %	93±5	93±4	89±8	92±4	91±7	0.000	0.022
Mixed venous oxygen saturation (n = 754), %	63±11	66±10	62±11	60±10	65±9	0.003	0.911
Functional capacity							
NYHA mean (n = 834)	2.9±0.7	2.7±0.5	3.0±0.7	3.0±0.7	3.0±0.7	0.139	0.764
6MWD (n = 785), m	362±137	377±149	305±127	365±138	357±144	0.003	0.476
Outcome by December 31, 2012							
Follow-up days	1,393±1,337	973±1,081	974±871	1,313±1,158	978±933		
Alive	271 (52)	22 (63)	58 (46)	138 (55)	16 (46)		
Dead	191 (37)	8 (23)	52 (42)	58 (23)	12 (34)		
Lung transplantation	20 (4)	0	6 (5)	4 (2)	5 (14)		
Lost to follow-up	34 (7)	5 (14)	8 (6)	15 (6)	2 (6)		

Data are given as means ± SD or numbers with percentages in parentheses.

cident cases were included. This article describes the changing epidemiology of the PH disease spectrum over predefined time periods.

Changes in PH Epidemiology over Time

The registry survived different PH classifications according to the WHO [1, 19]; however, for the vast majority of patients the 5 diagnostic groups as specified by the registry still apply. Over all PH groups, age increased over time and the predominance of females decreased towards an almost equal gender distribution during the last incident period. The same trend was found for PAH. This is in line with others, which also found that age at diagnosis increased from a mean age of 34 years in the NIH cohort to around 55 in French, British and American cohorts [7–9, 14–16, 21]. The mean age of CTEPH also increased over time periods; however, the significance could be attributed to the time before 2000, where also incident patients were included. Overall, age in our CTEPH cohort was comparable to the ASPIRE cohort (63 ± 14 vs. 70 ± 12 and 63 ± 16 years for not operated and nonoperable patients, respectively) and the international CTEPH registry (63 years) [11]. Overall, the BMI increased over incident time periods but not if PAH, CTEPH and PH in lung diseases were analyzed separately.

Among all PH patients registered, the percentage of PAH group I decreased over the incident time periods, whereas other groups increased. This is most probably related to an increased awareness by treating physicians of severe PH in heart, lung and thromboembolic diseases. Since the Swiss PH registry was kept by PH referral centers, the majority of PH due to chronic heart and lung diseases had severe PH and thus may not represent the whole spectrum of these two groups. Within the PAH group I, the percentage of adult patients with idiopathic PAH increased, whereas associated PAH slightly decreased. One reason for the decrease in associated PAH might be attributed to the lower number of children registered recently. The percentage of idiopathic (including heritable) PAH was slightly higher compared to the French registry, the percentage of portal hypertension and HIV-associated PAH was clearly lower (5 and 7% vs. 10 and 6%), with an even greater difference when looking at incident cases during similar time periods (4 and 3% vs. 15 and 10%) [16]. In comparison to the REVEAL registry [9], our proportion of idiopathic cases was slightly higher (60 vs. 46%) and that of congenital heart disease-associated PAH lower. It is not known whether these differences can be attributed to referral or diagnostic biases or whether they reflect true epidemiological differences between different countries.

Differences in PH Disease Characteristics

The majority of patients registered were in NYHA class III, and there were no differences between the major diagnostic groups and time periods. This is in line with other registries including different PH classifications [7]. However, the percentage of NYHA class I and II patients vastly differs between registries, e.g. 1/4 of patients in our cohort and the French registry, 1/6 in the UK registry, >1/3 in the REVEAL registry and 1/5 in the ASPIRE registry [7–9, 16]. The overall mean 6MWD at diagnosis was 357 m, with comparable values for most PH groups with the exception of PH due to patients with chronic lung diseases, who walked significantly less. This is in line with other registries including patients over all NYHA classes [8, 9]. The overall mPAP and PVR were in line with other registries [7]. The mPAP of the PAH group was slightly lower compared to that of the REVEAL and UK registries (48 vs. 55 and 54 mm Hg) [8, 9] and in line with incident PAH patients in the French registry [16]. The mPAP and PVR significantly decreased over incident periods, whereas the peripheral blood pressure increased. Both the mPAP and the cardiac output were significantly higher in PAH compared with CTEPH, resulting in a similar PVR. A higher cardiac output in PAH than in CTEPH was also found in the ASPIRE and Spanish registries [7, 10]. The arterial oxygen saturation was significantly lower in CTEPH than PAH and lowest in PH due to lung diseases. The mixed venous oxygen saturation was similar in our PAH compared to other PAH registries [8, 16].

PH Target Therapies by Diagnostic Group

In 59% of the PAH patients, target therapy was started with one drug, 10% received initial double and 3% triple combination therapy. The majority started with ERA or PDE5-I (52 or 22%), with increasing proportions over time, prostanoids were initially given in 14%, with a decreasing proportion over time. An initial CCB was given in 7% of all PAH cases with a decreasing proportion over time. Comparable trends for initial treatment changes were found in the British registry, with differences in absolute percentages of drug use, albeit time periods analyzed did not exactly correspond [8]. In comparison to British and American patients, PAH-specific therapy in Switzerland is more often started with an ERA and slightly less frequently with PDE5-I and prostanoids [8, 9, 21]. Out of all adult PAH patients registered over the entire

period, 89% received PAH target therapies, from these 43% combination therapies. The overall proportion is comparable to that of the ASPIRE registry, but Swiss patients received more combination therapies (26 vs. 46%) [7].

Out of all 249 CTEPH patients registered, only 34 (14%) had endarterectomy with a slightly increasing rate over time. Four patients underwent lung transplantation in earlier periods. Unfortunately, the registry does not provide whether this major part of nonoperated CTEPH patients was surgically inaccessible or which other reasons resulted in conservative management. This should be analyzed in the future. The percentage of nonoperated CTEPH patients is herewith strikingly higher compared with other registries and warrants medical action [7, 10, 11]. One reason might be the absence of a dedicated pulmonary endarterectomy center during that time in Switzerland, a small country with 8 million inhabitants potentially below the critical yearly case number. Nevertheless, major PH centers in Switzerland work in close collaboration with pulmonary endarterectomy centers in adjacent countries [11, 22]. However, treatment abroad for a very serious surgery might not be accepted by Swiss patients or insurance providers and be associated with administrative burdens for caregivers. 73% of the nonoperated CTEPH patients received PAH target therapies within 3 months of diagnosis, hereof 8% combination therapies, with increasing percentage over time. The majority of the nonoperated CTEPH patients received ERA, fewer PDE5-I and prostanoids. This is in line with other registries [7, 11].

Of PH cases due to lung disease registered, half started off-label PAH target therapy and 6% even combination therapy. Over the whole period, the proportion treated with PAH target therapy increased to 71% and was herewith higher than in the ASPIRE registry (47%) [7].

Event-Free Survival

In all diagnostic groups, event-free survival was significantly better for the first period including prevalent patients compared to later periods with incident cases. This is known from other registries which showed a better prognosis of prevalent cases due to selection bias [6, 23]. Our registry provides data from different PH classifications over predefined time periods. In all diagnostic groups, event-free survival was similar over incident periods. When looking only at PAH, event-free survival has been better since 2005, despite the higher ages of the patients. This might be explained by emerging treatment options, an increased awareness of the disease or a better care. The survival in the Swiss PAH collective was comparable to that of other registries [8, 9, 16].

The overall survival in nonoperated CTEPH patients was lower compared with cohorts reported from Sheffield or Spain, where half of the patients were operated [7, 10], but comparable to nonoperated patients [7, 24]. This clearly indicates that Switzerland has to make a clear effort to get more patients operated.

As in other cohorts, survival of patients with PH due to lung diseases was worse compared to other PH groups and comparable with the ASPIRE cohort, one of the few cohorts reporting on this group [7].

It has been known for a long time that severe PH is rare but associated with a dismal prognosis in lung disease [25, 26]. With an mPAP of 40 mm Hg, the PH in lung disease reported here, these patients were severely affected. Of these patients, 70% received PH target therapy, although such therapies have never been studied in a randomized trial [27]. Part of the PH associated with the chronic obstructive lung disease collective of the ASPIRE registry was treated with PH target therapy, and an improved outcome in those who responded with PVR reduction could be demonstrated [28]. Their prognosis was clearly worse compared to other diagnostic groups. This finding underscores the need for research and well-designed trials in order to develop effective therapies for PH in lung diseases.

PH due to heart disease was classified in a very small group (3.6%) only. As in other registries, this group tended to have a better survival at the beginning; the small number does not allow conclusions from long-term survival analysis in this group.

Limitations

Registries are important to characterize populations, assess the burden of diseases and describe practice patterns. In contrast to a prospective study, registries do usually not provide a schedule of data entry or allow including patients only according to predefined data sets. Thus, this registry rather reflects the real world, and it may therefore be that classification and data quality vary between centers. Other limitations of registries are the following: due to lack of randomization, registry data are prone to confounders, selection bias, and thus, comparison between registries with different inclusion/exclusion criteria has to be made with caution.

Conclusion

Taken together, the long-term follow-up provided by the Swiss PH registry offers the opportunity for real-life epidemiological data. The data shown here emphasize that over time periods, incident PH patients are older with an equal sex distribution. Survival was better for PAH diagnosed since 2008 compared with earlier periods and better for PAH and CTEPH compared with PH due to lung disease. The vast majority of PAH and CTEPH patients were treated with PAH target therapies, 43% even with combination therapy.

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Financial Disclosure and Conflicts of Interest

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Erratum

The authors of the article entitled 'Long-term data from the Swiss pulmonary hypertension registry' [Respiration 2015;89:127–140, DOI: 10.1159/000370125] wish to publish the following correction. On page 127, the name of an author has been published incorrectly: Guido Domeninghetti should read Guido Domenighetti. The correct author list should be as follows:

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